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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,452	07/31/2001	Sun Ai Raillard	02-107410US	4651
30560	7590	02/05/2004	EXAMINER	
MAXYGEN, INC.			HUTSON, RICHARD G	
INTELLECTUAL PROPERTY DEPARTMENT			ART UNIT	
515 GALVESTON DRIVE			PAPER NUMBER	
RED WOOD CITY, CA 94063			1652	

DATE MAILED: 02/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,452	RAILLARD ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 October 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 74,76-79,81,91-95 and 104-116 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 74,76-79,81,91-95 and 104-116 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>920103</u> | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1652

DETAILED ACTION-

Applicants amendment of claims 74, 76, 91 and 92 and the addition of new claims 104-116, Paper of 10/27/2003, is acknowledged. Claims 74, 76-79, 81, 91-95 and 104-116 are at issue and are present for examination. Applicants' arguments filed on 10/27/2003, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

Applicants filing of information disclosure, Paper No. 3, filed 12/13/2001, is acknowledged. Applicants submission of a new 1449 listing the above references CJ thru CR, IDS of 10/27/2003, is acknowledged. Applicants submission of the additional IDS of 5/28/2003 is also acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 91, 94 and 95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 91, 94 and 95 are indefinite in that they are confusing in that claim 91 recites "...The nucleotide incorporating enzyme variant of claim 74, further comprising recursively recombining the plurality of nucleic acid segments". As the enzyme variant of claim 74 does not further comprise recursively recombining the plurality of nucleic acid segments, but rather the process by which the enzyme variant of claim 74 is identified comprises recursively recombining the plurality of nucleic acid segments, this claim is unclear and confusing. It is suggested that applicants amend to correct this confusion.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 74, 76-79, 81, 91-95, 104-116 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was stated in the previous office action as it applied to previous claims 74, 76-79, 81 and 88-95. In response to the rejection applicants have amended claims 74, 76, 91 and 92, cancelled claims 88-90 and added new claims 104-116 and traverse the rejection as it applies to the newly amended and added claims.

Art Unit: 1652

Applicants traverse this rejection on the basis that applicants invention is of the type that is difficult to expressly describe in structural terms and that the process by which the claimed variants are initially generated inherently provides such structural definition.

Thus applicants submit that they have claimed their invention with a set of product by process claims, as such is supported by case law. It is acknowledged that product-by process claims are capable of satisfying the written description requirement, however in the instant application, applicants claims to a nucleotide incorporating enzyme variant are not sufficiently described such that they meet the written description requirement of 35 USC 112 first paragraph. As previously stated, applicants specification does not provide a single representative species of the claimed nucleotide incorporating enzyme variants, nor is there any disclosure of any particular structure to function/activity relationship in any species. Given this lack of representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention and the mere description of the claimed nucleotide incorporating enzyme variants by the process by which they are "identified" is insufficient to describe any of the encompassed species.

Applicants further submit that the written description guidelines expressly suggest that Applicants claims satisfy the Written Description requirement in Example 10 in statements that "the applicants could overcome the written description rejection by substituting the claim with a product by process claim". Applicants argument is not found persuasive as applicants claims are not similar to hybridization claims, which infer

Art Unit: 1652

structure by reference to another sequence. Applicants claims provide no reasonable structural definition inherently, merely by virtue of being generated by a process, the specificity of which may also be an issue. Applicants inclusion of a "percent identity limitation " with respect to the parental enzymes from which the claimed variants are derived does not help applicants description of the claimed variants themselves since the percent identity to which applicants refer merely limit the structural relationship of two otherwise structurally undefined molecules.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 74, 76-79, 81, 91-95 and 104-116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Taq* DNA polymerase variant as taught by Brandis et al. (See 102 rejection below), does not reasonably provide enablement for any nucleotide incorporating enzyme variant that incorporates a non-natural or rare nucleotide analogue at least about 10% as efficiently as a naturally occurring nucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was stated in the previous office action as it applied to previous claims 74, 76-79, 81 and 88-95. In response to the rejection applicants have amended

Art Unit: 1652

claims 74, 76, 91 and 92, cancelled claims 88-90 and added new claims 104-116 and traverse the rejection as it applies to the newly amended and added claims.

Applicants traverse this rejection on the basis that applicants have enabled the claimed invention so that any person skilled in the art can make and use the invention without undue experimentation. Applicants properly submit those factors to be considered in determining whether undue experimentation is required, as summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Applicants further submit that with respect to factors (1) and (2), the quantity of experimentation necessary, and the amount of direction or guidance presented, respectively, the disclosure is replete with specific guidance as to how to make the claimed nucleotide incorporating variants using recombinant methods and how to screen for such variants. Applicants argument is not found persuasive because while applicants provide a number of such general methods, none of the methods taught are considered specific to the production of the claimed variants and thus the amount of guidance is minimal.

While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., encoding a nucleotide incorporating enzyme

Art Unit: 1652

variant with a specific function) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such specific guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not support the broad scope of the claims which encompass all modifications and fragments of any nucleotide incorporating enzyme because the specification does not establish: (A) regions of the protein structure which may be modified without effecting nucleotide incorporation activity; (B) the general tolerance of nucleotide incorporating enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a nucleotide incorporating enzyme with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Applicants further submit that with respect to factor (3) the presence or absence of working examples, the specification provides further guidance as to how to make the claimed variants in the example provided at page 57, line 22 to page 62, line 17. This guidance referred to as an example is also of the general nature such that it is not

Art Unit: 1652

specific enough to give the ordinary artisan specific information that is needed to enable the claimed invention. With respect to factors (4) and (5), the nature of the invention, and the state of the prior art, applicants continue to submit that the claimed invention can be readily made using recombination and screening methods that are well known in the art, however, as stated above applicants have merely presented general recombination and screening methods, that without additional specific details are not successful in enabling the claimed invention.

With respect to factor (6) the relative skill of those in the art, and factor (7) the predictability or unpredictability of the art, applicants submit that the use of the disclosed recombination and screening methods is standard practice to those who practice this art. While this is acknowledged, the it remains that additional guidance must be given to those who routinely practice such recombination and screening methods if one is to expect a specific outcome of such recombination and screening methods, i.e. the generation of nucleotide incorporating enzyme variants with specific properties.

With respect to factor 8) the breadth of the claim(s), applicants disagree that the claims are so broad as to encompass any nucleotide incorporating enzyme variant that incorporates any non-natural or rare nucleotide analogue at least about 10% as efficiently as a naturally occurring nucleotide because the claimed nucleotide incorporating enzyme variant is defined by structure as discussed above under applicants written description arguments. This two as above is not found persuasive because as discussed above and previously the process of identifying the claimed

Art Unit: 1652

nucleotide incorporating enzyme variant imparts little if any structure on the claimed nucleotide incorporating enzyme variant.

Finally applicants submit that recombination methods, which do not rely on a priori knowledge of structure/function relationships, are widely recognized as having been successfully applied to generate protein variants. While this is acknowledged, the use of such methods to generate protein variants with specific characteristics requires additional specific guidance which applicants have not presented, such that the genus of the claimed nucleotide incorporating enzyme variants are not enabled.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any nucleotide incorporating enzyme. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Art Unit: 1652

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 74, 76-79, 81, 88-95 and 104-116 are rejected under 35 U.S.C. 102(e) as being anticipated by Brandis et al. (U.S. Patent No. 6,265,193 B1).

This rejection was stated in the previous office action as it applied to previous claims 74, 76-79, 81 and 88-95.

Brandis et al. DNA polymerases having improved labeled nucleotide incorporation properties. Brandis et al. specifically teach a number of Taq DNA polymerase mutants which have at least a 2 fold reduced discrimination for fluorescein-type dye labeled nucleotides as compared with naturally occurring DNA polymerases. While it is admitted that Brandis et al. do not specifically measure the efficiency of incorporation of a fluorescein-type dye labeled nucleotide relative to a natural occurring nucleotide but rather they measure the efficiency of incorporation of a fluorescein-type dye labeled dideoxynucleotide relative to a unlabeled dideoxynucleotide, based on the results shown for the generated mutant DNA polymerases (See examples 2 and 4,

Tables 2 and 1) it is believed that this is an inherent property of the DNA polymerases taught by Brandis et al. Therefore claims 74, 76, 77-79, 81, 88-95 are anticipated by Brandis et al.

It is acknowledged that Brandis et al. do not produce the taught DNA polymerase mutants by the process(s) specified by applicants in the rejected claims, however the patentability of claims drawn to a nucleotide incorporating enzyme variant are not determined by the process by which the variant is made but rather by the nucleotide incorporating enzyme variant itself and thus the variants taught by Brandis et al. anticipate the claimed variants.

In response to the rejection applicants have amended claims 74, 76, 91 and 92, cancelled claims 88-90 and added new claims 104-116 and traverse the rejection as it applies to the newly amended and added claims.

Applicants traverse this rejection on the basis that the Brandis et al. patent does not describe, *inter alia*, the claimed features of the polynucleotide that encodes the variant, i.e. a polynucleotide that comprises segments encoding all or part of either two or more members of a family of parental RNA-dependent DNA polymerases...

Applicants argument is not found persuasive because as previously stated and repeated above, it is acknowledged that Brandis et al. do not produce the taught DNA polymerase mutants by the process(s) specified by applicants in the rejected claims, however the patentability of claims drawn to a nucleotide incorporating enzyme variant are not determined by the process by which the variant is made but rather by the

nucleotide incorporating enzyme variant itself and thus the variants taught by Brandis et al. anticipate the claimed variants.

Further applicants attention is directed to the referred to limitation "a polynucleotide that comprises segments encoding all or part of either two or more members of a family of parental RNA-dependent DNA polymerases". As a single amino acid is encompassed by "a part of a member of a family of parental RNA-dependent DNA polymerases" any nucleic acid which encodes "either two or more single amino acids" such as that polynucleotide which encodes the polymerase taught by Brandis et al. meets this limitation.

Thus claims 74, 76-79, 81, 88-95 and 104-116 are anticipated by Brandis et al.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

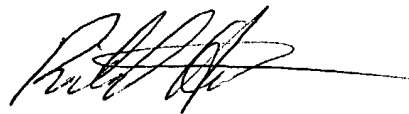
Art Unit: 1652

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

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1/28/2004